

## Bölüm 14

# ERKEN EVRE HORMON POZİTİF MEME KANSERİNDE ADJUVAN ANTİ-HORMONAL TEDAVİ

Ayşegül İLHAN<sup>1</sup>

### GİRİŞ

Meme kanseri, dünyada en sık teşhis edilen kanserdir ve kadınlarda kansere bağlı ölümlerin en sık nedenidir(1).Meme kanseri, fenotipik olarak çeşitli biyolojik alt tiplerden oluşan ve farklı davranış gösteren heterojen bir kanserdir. Östrojen(ER) ve/veya progesteron(PR) reseptörü pozitif meme kanseri sıklıkla görülen alt tipi olmakla beraber, ER ve PR durumu prognostik ve prediktif değere sahiptir. National Comprehensive Cancer Network (NCCN) kılavuzları tüm primer invaziv meme kanserlerinde ER ve PR durumunun belirlenmesini önermektedir(2). Hormon reseptörü pozitif olarak kabul edilmesi için ER / PR'nin tümör hücrelerinin minimum % 1'inde pozitif olması gerekmektedir(3). ER veya PR pozitif invaziv meme kanserinin adjuvan endokrin tedavisi hastanın yaşı, lenf nodu durumu, adjuvan kemoterapinin uygulanıp uygulanmadığına bakılmaksızın düşünülmelidir(4). Amaç meme kanserinin nüksünü önlemek ve mortalitesini azalmaktır.

### TEDAVİ YAKLAŞIMINA GENEL BAKIŞ

Adjuvan endokrin tedavi, hastanın premenopozal ya da postmenopozal duruma bağlı olduğundan hastanın menapoz durumunu belirlemek önemlidir. Tanı sırasında premenopozal olup adjuvan kemoterapi verilen hastanın amenoreik olması, menapoz durumunun güvenilir bir göstergesi değildir.

NCCN tarafından kullanılan menopoz tanımı için aşağıdakilerden birinin olması yeterlidir(5):

- 60 yaş ve üstü kadınlar veya
- Aşağıdaki koşullardan biri karşılayan 60 yaş altı kadınlar;
- Daha önce bilateral ooforektomi yapılan,
- Tamoksifen, kemoterapi veya over supresyonu öyküsü yokluğunda, 12 ay veya

**hastalar 5 yıl süreyle exemestan+OFS ve tamoksifen+OFS gruplarına randomize edildi(36). Exemestan+OFS grubunda DFS %92.8, tamoksifen+OFS grubunda %88.8'di ve her iki grup arasında sağkalım farkı yoktu, fakat exemestan+OFS ile adjuvan tedavi,tamoksifen+OFS ile tedaviye göre nüks riskini azalmıştı(37). Adjuvan endokrin tedavi süresi 5 yıldır fakat nüks riski yüksek hasta gruplarında uzatılmış endokrin tedavi gündeme gelmektedir.In the Worldwide Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) çalışmasına göre 5 yıl boyunca tamoksifen tedavisini tamamlamış erken meme kanseri olan 12894 kadına ek 5 yıl tamoksifen kullanmak meme kanserine bağlı ölüm riskinde ve nüks riskinde anlamlı azalmaya neden olmuştur(38).Ancak tamoksifen kullanıma bağlı endometrial kanser ve pulmoner emboli için göreceli riskte anlamlı artış görülmüştür(36). Adjuvant Tamoxifen To Offer More (aTTom) çalışmasının ön sonuçları ise 10 yıl tamoksifen kullanımının meme kanseri nüksü ve ölüm oranlarında azalmaya neden olduğunu desteklemiştir(39).**

Sonuç olarak; güncel tedavi klavuzları premenapozal erken evre hormon pozitif meme kanserli kadın hastalarda adjuvan tedavide 5 yıl tamoksifen (kategori 1) +/- OFS veya OFS ile beraber aromataz inhibitörü (kategori 1) kullanımını önermektedir (28).

## KAYNAKLAR

1. Forouzanfar MH, Foreman KJ, Delossantos AM. Breast and cervical cancer in 187 countries-between 1980 and 2010: a systematic analysis. *Lancet Oncol*, 2011 Oct 22;378(9801):1461-84, doi: 10.1016/S0140-6736(11)61351-2. Epub 2011 Sep 14.
2. Allred DC, Carlson RW, Berry DA. NCCN Task Force Report: Estrogen Receptor and Progesterone Receptor Testing in Breast Cancer by Immunohistochemistry. *J Natl Cancer Inst*, 2009 Sep;7 Suppl 6:S1-S21; quiz S22-3.
3. Hammond ME, Hayes DF, Dowsett M, Allred DC. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*, 2010 Jun 1;28(16):2784-95. doi: 10.1200/JCO.2009.25.6529. Epub 2010 Apr 19.
4. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet Oncol*, 1998 May 16;351(9114):1451-67.
5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Breast Cancer (version 1.2014). [http://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf) (Accessed on January 28, 2014).
6. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. *N Engl J Med*, 2003; 348:2431.
7. Coombes RC, Kilburn LS, Snowdon CF. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet Oncol*, 2007 Feb 17;369(9561):559-70.
8. Kaufmann M, Jonat W, Hilfrich J. Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 Study. *J Clin Oncol*, 2007 Jul 1;25(19):2664-70. Epub 2007 Jun 11.

9. Early breast cancer trialists' collaborative group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet Oncol*, 2015;386:1341-52.
10. Goss PE<sup>1</sup>, Ingle JN, Martino S. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst*, 2005 Sep 7;97(17):1262-71.
11. Baum M, Budzar AU, Cuzick J. ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet Oncol*, 2002 Jun 22;359(9324):2131-9.
12. Howell A, Cuzick J, Baum M. ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet Oncol*, 2005 Jan 1-7;365(9453):60-2.
13. Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group, Howell A, Tobias JS. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol*, 2008 Jan;9(1):45-53.
14. Duffy S, Jackson TL, Lansdown M. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial: first results of the endometrial sub-protocol following 2 years of treatment. *Hum Reprod*, 2006 Feb;21(2):545-53. Epub 2005 Oct 6.
15. Fallowfield L, Cella D, Cuzick J. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. *J Clin Oncol*, 2004 Nov 1;22(21):4261-71.
16. Eastell R, Adams JE, Coleman RE, Clack G. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J Clin Oncol*, 2008 Mar 1;26(7):1051-7. doi: 10.1200/JCO.2007.11.0726.
17. Cuzick J, Sestak I, Baum M et al. on behalf of the ATAC/LATTE investigators. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol*, 2010; 11: 1135-1141
18. Breast International Group (BIG) 1-98 Collaborative Group, Thürlimann B, Keshaviah A. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med*, 2005 Dec 29;353(26):2747-57.
19. Rabaglio M, Sun Z, Price KN. Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial. *Ann Oncol*, 2009 Sep;20(9):1489-98. doi: 10.1093/annonc/mdp033. Epub 2009 May 27.
20. Regan MM, Neven P, Giobbie-Hurder A. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8.1 years median follow-up. *Lancet Oncol*, 2011 Nov;12(12):1101-8. doi: 10.1016/S1470-2045(11)70270-4. Epub 2011 Oct 20.
21. Jonat W, Gnani M, Boccardo F. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. *Lancet Oncol*, 2006 Dec;7(12):991-6.
22. Van de Velde CJ, Rea D, Seynaeve C. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. *Lancet Oncol*, 2011 Jan 22;377(9762):321-31. doi: 10.1016/S0140-6736(10)62312-4.
23. BIG 1-98 Collaborative Group, Mouridsen H, Giobbie-Hurder A. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. *N Engl J Med*, 2009 Aug 20;361(8):766-76. doi: 10.1056/NEJMoa0810818.
24. Jin H, Zhao N, Shepherd LE, Goss PE. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. *J Clin Oncol*, 2012;30(79):718.
25. R. Jakesz, H. Samonigg, R. Greil. Extended Adjuvant Therapy With Anastrozole Among Postmenopausal Breast Cancer Patients: Results From the Randomized Austrian Breast and Colo-

- rectal Cancer Study Group Trial 6a. *Journal of the National Cancer Institute*, Volume 99, Issue 24, 19 December 2007, Pages 1845–1853.
26. Goss PE, Ingle JN, Pritchard KI. Extending Aromatase-inhibitor Adjuvant Therapy to 10 Years. *N Engl J Med*, 2016;375(3):209.
  27. Mamounas EP, Bandos H, Lembersky BC. A randomised, double-blinded, placebocontrolled clinical trial of extended adjuvant endocrine therapy (tx) with letrozole (L) in postmenopausal women with hormone-receptor (+) breast cancer (BC) who have completed previous adjuvant tx with an aromatase inhibitor (AI): Result from NRG Oncology/NSBAP B-42.SAABCS 2016. abst no:S1-05.
  28. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Breast Cancer (version 1.2019). [http://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf) (Accessed on June 9, 2019).
  29. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Cancer Stat Facts: Female breast cancer. <http://seer.cancer.gov/statfacts/html/breast.html> (Accessed on April 16, 2019).
  30. Eifel P, Axelson JA, Costa J. National Institutes of Health Consensus Development Conference Statement: adjuvant therapy for breast cancer, November 1-3, 2000. *J Natl Cancer Inst*, 2001;93:979-989.
  31. Goldhirsch A, Glick JH, Gelber RD. Meeting highlights: International Consensus Panel on the Treatment of Primary Breast Cancer. *J Clin Oncol*, 2001;19:3817-3827.
  32. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet Oncol*, 2005 May 14-20;365(9472):1687-717.
  33. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet Oncol*, 2011 Aug 27;378(9793):771-84. doi: 10.1016/S0140-6736(11)60993-8. Epub 2011 Jul 28.
  34. LHRH-Agonists in Early Breast Cancer Overview Group. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet Oncol*, 2007;369:1711-1723.
  35. Griggs JJ, Somerfield MR, Anderson H. American Society of Clinical Oncology endorsement of the Cancer Care Ontario practice guideline on adjuvant ovarian ablation in the treatment of premenopausal women with early-stage invasive breast cancer. *J Clin Oncol*, 2011;29:3939-3942[Erratum, *J Clin Oncol* 2012;30:1398.].
  36. Francis PA, Regan MM, Fleming GF. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med*, 2015 Jan 29;372(5):436-46. doi: 10.1056/NEJMoa1412379. Epub 2014 Dec 11.
  37. Pagani O, Regan MM, Walley BA. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med*, 2014 Jul 10;371(2):107-18. doi: 10.1056/NEJMoa1404037. Epub 2014 Jun 1.
  38. Davies C, Pan H, Godwin J, Gray R. Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet Oncol*, 2013 Mar 9;381(9869):805-16.
  39. Gray R, Rea D, Hanley K. aTTom:Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer ( abstract). *J Clin Oncol*, 2013;31(suppl):Abstract 5.Avaible at.